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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/640,852	08/17/2000	Alissar Nehme	600-41-PA	5392

7590 02/13/2002

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EXAMINER
LANDSMAN, ROBERT S

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/640,852	NEHME ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communicati n appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-13, drawn to a pharmaceutical composition, classified in class 436, subclass 91.

II. Claims 14-30, drawn to a method of treating a malignant disease, classified in class 514, subclass 1.

B. The inventions are distinct, each from each other because of the following reasons:

Inventions I and II are related as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product, or (2) the product as claimed can be used in a materially different process of using that product MPEP § 806.05(h). In the instant case the pharmaceutical composition can likely be used for the treatment of viral diseases.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter as defined by MPEP § 808.02, the Examiner has *prima facie* shown a serious burden of search (see MPEP § 803). Therefore, an initial requirement of restriction for examination purposes as indicated is proper.

C. A telephone call was made to Gabor Szekeres on July 25, 2001 to request an oral election to the above restriction. Applicant's election of Group II, claims 14-30, is acknowledged with traverse.

Applicant is reminded that upon cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR § 1.48(b) and by the fee required under 37 CFR § 1.17 (h).

2. Formal Matters

A. Claims 1-30 are pending in the application and were subject to restriction. On July 25, 2001 Gabor Szekeres orally elected Group II, claims 14-30 with traverse. However, after further consideration, the Examiner has withdrawn the restriction requirement since the pharmaceutical compositions of non-elected Group I would be required to practice the invention of elected Group II. Therefore, claims 1-30 will be examined.

3. Claim Objections

A. Claim 1 is objected to since there should be a semi-colon between the phrases "imidazolyl and" and "B is COOH."

B. Claim 1 is objected to since there should be commas around the word "independently."

C. Claims 3 and 4 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 2. Claims 7 and 8 are substantial duplicates of claim 6. Claims 11 and 12 are substantial duplicates of claim 10. Claims 16-18 are substantial duplicates of claim 15. Claims 22 and 23 are substantial duplicates of claim 21. Claims 28 and 29 are substantial duplicates of claim 27. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 3, 4, 7, 8, 11, 12, 16-18, 22, 23, 28 and 29 all recite either pharmaceutical compositions, or methods using these compositions in which the compositions, or methods, are adapted for breast cancer or leukemia. However, these claims do not recite any additional limitations to said compositions or methods of claims 2, 6, 10, 15, 21 and 27, from which these claims depend. These are intended use claims and do not necessarily alter the contents of the compositions.

4. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of Formula 3 (tazarotene) and interferon in SK-BR-3, T-47D and HL-60 cells, does not reasonably provide enablement for methods of treating **any malignant diseases** in a mammal,

including breast cancer and leukemia by administering any of the compounds (**"formulas" and all other "chemotherapeutic agents"**) recited in the claims, or **pharmaceutical compositions** thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claims is excessive. Applicants are only enabled for the use of tazarotene in combination with interferon in SK-BR-3, T-47D and HL-60 cells. However, Applicants are claiming methods of treating any and all malignant diseases by administering an effective dose of the compound ("formula") of claim 14, 19 or 24, or pharmaceutical compositions thereof as recited in claims 1, 5 and 9 in combination with either interferon or any other chemotherapeutic agent and which can be "**adapted**" to treat these diseases. The cell lines used, as defined on page 9, lines 10-15 of the specification, are breast cancer and leukemia cell lines and do not represent all "malignant diseases." Applicants have only provided guidance and working examples of the use of tazarotene (Formula 3 of the specification) in combination with interferon to provide anti-proliferative effects in SK-BR-3, T-47D and HL-60 cells. Not only have Applicants not demonstrated the anti-proliferative effects of any other compound besides tazarotene in combination with interferon in the specification (Figures 1-16), but they have not demonstrated the use of any compounds including tazarotene and other chemotherapeutic agents to treat any and all malignant diseases in a mammal. Applicants have shown no nexus between the *in vitro* data using SK-BR-3, T-47D and HL-60 cells and *in vivo* experiments in mammals, nor have they enabled any and all pharmaceutical compositions comprising any of the claimed compounds for use in treating any malignant diseases.

Additionally, Applicants have provided no guidance or working examples of how these pharmaceutical compositions will be administered, or how these methods will be performed, to treat such malignancies as brain cancer, in which the **blood-brain barrier** will limit the compounds which can be used, as well as the routes of administration for these compounds. For example, as seen in claim 30, it would not be expected that a dose of 500mg of drug would be able to be injected into a brain tumor on a daily (or even a one-time) basis, especially without guidance of how to successfully perform such a task.

Furthermore, not only would it not be predictable to the artisan how to make pharmaceutical compositions of all the claimed compounds in order to treat mammals with any and all malignant diseases, including breast cancer and leukemia (e.g. no treatment regimen, route of administration), but it would not be predictable how to treat any and all of the claimed diseases using these pharmaceutical compositions, including breast cancer and leukemia, since Applicants have only provided *in vitro* data for these two types of cancer cell lines.

Therefore, in summary, due to the excessive breadth of the claims regarding pharmaceutical compositions and methods to treat any and all malignant diseases in mammals, along with the lack of guidance and working examples of these pharmaceutical compositions and their use in treating mammals as well as the unpredictability to one of ordinary skill in the art how to make and use these pharmaceutical compositions to treat any and all malignant diseases in mammals, leads the Examiner to conclude that undue experimentation is necessary to practice the invention as claimed.

5. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 14-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1 and 14 are indefinite since the variable "X" in these structures is not defined in the claim. Claims 2-4 and 15-18 are rejected since they depend from these rejected base claims.

B. Claims 1 and 14 are vague and indefinite since the metes and bounds of "therapeutically effective dose" are not defined. Applicants are claiming numerous pharmaceutical compositions, including the claimed "formulas" and other "chemotherapeutic agents" to treat all malignant diseases in mammals and Applicants have provided no dosing ranges for all of these compounds, alone or in combination, to treat all of the claimed diseases.

6. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 1-3, 5-7, 9-11, 13-17, 19-22, 24-28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable by Chandraratna (US Patent No. 5,045,551; 5,602,130; 6,090,826 – all of these references are on the Form PTO 1449 submitted 11/16/00) each in view of Marth et al. (JNCI 77:1197-1202, 1986 – this reference is on the Form PTO 1449 submitted 11/16/00). The claims recite pharmaceutical compositions and methods for the treatment of a malignant disease, including breast cancer, by providing a therapeutically effective dose of the claimed compounds in combination with another chemotherapeutic agent, including human recombinant interferon.

Chandraratna (US Patent No. 5,045,551; 5,602,130; 6,090,826) teaches compounds which are identical to those to the compounds of the claimed invention (claims 1, 5, 9, 14, 19 and 24) and that these compounds can be used to treat cancers and "malignant hyperproliferative diseases (Patent 5,045,551, column 1, lines 34-61; Patent 5,602,130, column 4, lines 5-48 and claim 15; Patent 6,090,825, column 2, line 28 – column 3, line 42). Though Chandraratna does not specifically teach administering the compounds of US Patent No. 5,045,551, 5,602,130 and 6,090,826 at doses of approximately 50 mg to 500 mg daily, it would have been obvious to have identified the optimum dosing range for a subject. In fact, Chandraratna does teach that "a given therapeutic concentration will vary from condition to condition...and will best be determined at the time and place through routine experimentation." (column 4, line 59 – column 5, line 5 of US Patent No. 5,045,551; column 5, lines 22-37 of US Patent No. 5,602,130; and column 7, lines 10-26 of US Patent No. 6,090,826). Chandraratna does not teach pharmaceutical compositions comprising the compounds of the claimed invention in combination with another chemotherapeutic agent, such as recombinant human interferon to treat such diseases such as breast cancer.

However, Marth et al. do teach the use of recombinant human interferon-γ in combination with other compounds (retinoic acid) to inhibit several human mammary carcinoma (i.e. breast cancer) cell lines (Abstract and Figures 1-6). It would, therefore, have been obvious to one of ordinary skill in the art at the time of the invention to have substituted the compounds of any of the Chandraratna patents for retinoic acid in the composition of Marth et al. for use to treat a malignant disease such as breast cancer.

First, Marth et al. teach that combinations of RA and interferon can act either additively, or synergistically to inhibit the growth of breast cancer cells, providing motivation for combining various compounds. Therefore, the artisan would have been motivated to have combined two compounds, each with known anticancer effects, for use as a pharmaceutical composition in the treatment of various malignant diseases, including breast cancer. In addition, the artisan would have had a reasonable expectation of success in treating a patient with this combination since both the compounds of Chandraratna and Marth et al. were well-known at the time of the invention to each inhibit the proliferative effects of various tumors.

B. Claims 1, 2, 4-6, 8-10, 12-30 are rejected under 35 U.S.C. 103(a) as being unpatentable by Chandraratna (US Patent No. 5,045,551; 5,602,130; 6,090,826 – all of these references are on the Form PTO 1449 submitted 11/16/00) each in view of Nara (Leuk Lymphoma. 1993 Jun;10(3):201-7). The claims recite pharmaceutical compositions and methods for the treatment of a malignant disease, including leukemia, by providing a therapeutically effective dose of the claimed compounds in combination with another chemotherapeutic agent, including human recombinant interferon.

Chandraratna (US Patent No. 5,045,551; 5,602,130; 6,090,826) teaches compounds which are identical to those to the compounds of the claimed invention (claims 1, 5, 9, 14, 19 and 24) and that these compounds can be used to treat cancers and "malignant hyperproliferative diseases (Patent 5,045,551, column 1, lines 34-61; Patent 5,602,130, column 4, lines 5-48 and claim 15; Patent 6,090,825, column 2, line 28 – column 3, line 42). Though Chandraratna does not specifically teach administering the compounds of US Patent No. 5,045,551, 5,602,130 and 6,090,826 at doses of approximately 50 mg to 500 mg daily, it would have been obvious to have identified the optimum dosing range for a subject. In fact, Chandraratna does teach that "a given therapeutic concentration will vary from condition to condition...and will best be determined at the time and place through routine experimentation." (column 4, line 59 – column 5, line 5 of US Patent No. 5,045,551; column 5, lines 22-37 of US Patent No. 5,602,130; and column 7, lines 10-26 of US Patent No. 6,090,826). Chandraratna does not teach pharmaceutical compositions comprising the compounds of the claimed invention in combination with another chemotherapeutic agent, such as recombinant human interferon to treat such diseases such as lymphoma.

Nara teaches that interferon-γ alone, or in combination with other agents, such as TNF-α, suppress terminal divisions and self-renewal of leukemic blast progenitors from acute myeloblastic leukemia (AML) patients (Abstract; Table 1; Figures 1 and 2). It would, therefore, have been obvious to

one of ordinary skill in the art at the time of the invention to have substituted other chemotherapeutic agents, such as the compounds of any of the Chandraratna patents for TNF-α in the composition of Nara for use to treat a malignant disease such as leukemia since it was well-known at the time of the invention that interferon-γ alone, or in combination with other agents could inhibit blast progenitor growth in AML patients. The artisan would have had a reasonable expectation of success in treating a patient with this combination since both the compounds of Chandraratna and Nara were well-known at the time of the invention to each inhibit the proliferative effects of various tumors.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
February 11, 2002

Gary L. Kunz
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